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(54) HARD GELATIN CAPSULE AGENT HAVING IMPROVED DISSOLUTION PROPERTY

(57)Abstract:
PROBLEM TO BE SOLVED: To suppress the insolubilization of gelatin and improve the dissolution property of an active component by including aminoacetic acid in the agent filled in a capsule.
SOLUTION: Aminoacetic acid is included in an agent filled in a hard gelatin capsule. The amount of the aminoacetic acid is preferably 0.5-30 wt.% based on the shell of the capsule. The capsule agent preferably contains a condensed imidazopyridine derivative, etc., such as 2-(isoxazol-3-yl)-1,6,7,9- tetrahydroimidazo[4,5-d]pyrano[4,3-b]pyridine as an active pharmaceutical component in an amount of 0.1-40 wt.% based on the whole capsule agent and 5-150 wt.% based on the shell of the capsule. The capsule shell is preferably incorporated with 30-60 wt.% of a disintegration agent (e.g. carboxymethyl cellulose).

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* NOTICES *

CLAIMS

[Claim(s)]

[Claim 1] A ** gelatine capsule agent which is characterized by containing aminoacetic acid in an encapsulation object and by which elution nature has been improved.
[Claim 2] Pharmaceutical preparation according to claim 1 which contains aminoacetic acid 0.5 to 30% of the weight to a capsule hide.
[Claim 3] Pharmaceutical preparation according to claim 1 or 2 which contains a condensation imidazo pyridine derivative as a physic active ingredient.
[Claim 4] Pharmaceutical preparation according to claim 3 whose condensation imidazo pyridine derivatives are -1, 6 and 7, 2-(isoxazole-3-IRU) tetrahydroimidazo [9-] [4 and 5-d] PIRANO [4 and 3-b] pyridine, salts permitted on the medicine manufacture, or those hydrates.

[Claim 5] Pharmaceutical preparation according to claim 4 which contains aminoacetic acid one to 20% of the weight to a capsule hide.
[Claim 6] Pharmaceutical preparation of claim 5 ** which contains disintegrator 30 to 60% of the weight to a capsule hide.
[Claim 7] Pharmaceutical preparation according to claim 4 which contains -1, 6 and 7, 2-(isoxazole-3-IRU) tetrahydroimidazo [9-] [4 and 5-d] PIRANO [4 and 3-b] pyridine, salts permitted on the medicine manufacture, or those hydrates ten to 50% of the weight to a capsule hide, and contains disintegrator for aminoacetic acid 30 to 60% of the weight one to 20% of the weight.
[Claim 8] Pharmaceutical preparation according to claim 4 to 7 whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 40 degrees C / 75% disconnection of relative humidity is 60% or more.
[Claim 9] Pharmaceutical preparation according to claim 8 this whose rate of elution is 70% or more.
[Claim 10] Pharmaceutical preparation according to claim 8 this whose rate of elution is 80% or more.
[Claim 11] Pharmaceutical preparation according to claim 4 to 7 it is twice [more than] whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 40 degrees C / 75% disconnection of relative humidity of this as compared with contrast pharmaceutical preparation which does not contain aminoacetic acid.
[Claim 12] Pharmaceutical preparation according to claim 7 in which a rate of elution according to claim 11 is shown.
[Claim 13] Pharmaceutical preparation according to claim 1 or 2 which contains a benzothiazepine derivative as a physic active ingredient.
[Claim 14] Pharmaceutical preparation according to claim 13 whose benzothiazepine derivatives are salts permitted on (2S-cis-)-3-acetoxy-5-[3-(4-(2-methoxypheny)-1-piperazinyl) propyl]-2, 3-dihydro-2-(4-methoxypheny)-8-chloro -1, 5-benzothiazepine-4

(5H)-ON, and its medicine manufacture, or those hydrates.
[Claim 15] Pharmaceutical preparation according to claim 14 which contains aminoacetic acid one to 20% of the weight to a capsule hide.
[Claim 16] Pharmaceutical preparation according to claim 15 which contains disintegrator 60 to 90% of the weight to a capsule hide.
[Claim 17] As opposed to a capsule hide (2S-cis-)-3-acetoxy-5-[3-(4-(2-methoxypheny)-1-piperazinyl) propyl]-2, 3-dihydro-2-(4-methoxypheny)-8-chloro -1, 5-benzothiazepine-4 (5H)-ON, Pharmaceutical preparation according to claim 14 which contains salts permitted on the medicine manufacture, or those hydrates 60 to 100% of the weight, and contains disintegrator for aminoacetic acid 60 to 90% of the weight one to 20% of the weight.
[Claim 18] Pharmaceutical preparation according to claim 14 to 17 whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 45 degrees C / sealing is 60% or more.
[Claim 19] Pharmaceutical preparation according to claim 18 this whose rate of elution is 70% or more.
[Claim 20] Pharmaceutical preparation according to claim 18 this whose rate of elution is 80% or more.
[Claim 21] Pharmaceutical preparation according to claim 14 to 17 whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 45 degrees C / sealing is 1.5 or more times as compared with contrast pharmaceutical preparation which does not contain aminoacetic acid.
[Claim 22] Pharmaceutical preparation according to claim 17 in which a rate of elution according to claim 21 is shown

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] This invention relates to the ** gelatine capsule agent by which the elution nature of a chief remedy has been improved.
[0002]
[Description of the Prior Art] A ** gelatine capsule agent has the trouble that gelatin starts and insolubilizes aging, such as bridge formation and a polymerization, between intramolecular or a molecule, consequently the emission nature of an endocyst drug is delayed remarkably in the mothball middle class, when the amino group in the gelatin which is a capsule hide causes amino-carbonyl reactions, such as reducing sugar in packing, other aldehydes, and a Maillard reaction. As a means to solve such a problem conventionally, the method of blending various kinds of protein, amino acid, the material of amino-group content, or an anti-oxidant into an encapsulation object is indicated by JP,49-599817,A, and aminoacetic acid (glycine) is also indicated as an example of amino acid. However, the example of the ** gelatine capsule agent which blended aminoacetic acid is not indicated. Moreover, the method of blending a free radical trapping agent into an encapsulation object is indicated as a means to prevent insolubilization of a ** gelatine capsule agent by JP,8-99869,A. This technology is not the means which prevents generating of the free radical used as the generation source of peroxides, such as aldehydes, and carries out direct inhibition of the above amino-carbonyl reaction itself by the free radical trapping agent. Moreover, aminoacetic acid is not indicated as an example of a free radical trapping agent.
[0003]
[Problem(s) to be Solved by the Invention] Insolubilization of gelatin was controlled and development of the new ** gelatine capsule agent by which the elution nature of a chief remedy has been improved was demanded.
[0004]
[Means for Solving the Problem] When making aminoacetic acid live together in packing of a ** gelatine capsule agent as a result of this invention persons' inquiring wholeheartedly in view of the above-mentioned technical problem, this invention which shows that insolubilization of gelatin is controlled and the elution nature of a chief remedy is improved to a header and the following was completed.
(1) A ** gelatine capsule agent which is characterized by containing aminoacetic acid in an encapsulation object and by which elution nature has been improved (henceforth this capsule).
(2) Pharmaceutical preparation of one above-mentioned publication which contains aminoacetic acid 0.5 to 30% of the weight to a capsule hide.
(3) Pharmaceutical preparation of the above 1 or 2 publications which contain a condensation imidazo pyridine derivative as a physic active ingredient.
(4) Pharmaceutical preparation of three above-mentioned publication whose condensation imidazo pyridine derivatives are -1, 6 and 7, 2-(isoxazole-3-IRU) tetrahydroimidazo [9-] [4 and 5-d] PIRANO [4 and 3-b] pyridine, salts permitted on the medicine manufacture, or those hydrates.
(5) Pharmaceutical preparation of four above-mentioned publication which contains

aminoacetic acid one to 20% of the weight to a capsule hide.
(6) Pharmaceutical preparation of the above-mentioned 5 ** which contain disintegrator 30 to 60% of the weight to a capsule hide.
(7) Pharmaceutical preparation of four above-mentioned publication which contains -1, 6 and 7, 2-(isoxazole-3-IRU) tetrahydroimidazo [9-] [4 and 5-d] PIRANO [4 and 3-b] pyridine, salts permitted on the medicine manufacture, or those hydrates ten to 50% of the weight to a capsule hide, and contains disintegrator for aminoacetic acid 30 to 60% of the weight one to 20% of the weight.
(8) Pharmaceutical preparation according to claim 4 to 7 whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 40 degree C / 75% disconnection of relative humidity is 60% or more.
[0005] (9) Pharmaceutical preparation of eight above-mentioned publication this whose rate of elution is 70% or more.
(10) Pharmaceutical preparation of eight above-mentioned publication this whose rate of elution is 80% or more.
(11) Pharmaceutical preparation given in either of the above 4-7 it is twice [more than] whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 40 degree C / 75% disconnection of relative humidity of this as compared with contrast pharmaceutical preparation which does not contain aminoacetic acid.
(12) Pharmaceutical preparation given in the above 7 which shows a rate of elution of a publication to the above 11.
(13) Pharmaceutical preparation given in the above 1 or 2 which contains a benzothiazepine derivative as a physic active ingredient.
(14) Pharmaceutical preparation of 13 above-mentioned publication whose benzothiazepine derivatives are salts permitted on (2S-cis-)-3-acetoxy-5-[3-(4-(2-methoxypheny)-1-piperazinyl) propyl]-2, 3-dihydro-2-(4-methoxypheny)-8-chloro -1, 5-benzothiazepine-4 (5H)-ON, and its medicine manufacture, or those hydrates.
(15) Pharmaceutical preparation of 14 above-mentioned publication which contains aminoacetic acid one to 20% of the weight to a capsule hide.
[0006] (16) Pharmaceutical preparation of 15 above-mentioned publication which contains disintegrator 60 to 90% of the weight to a capsule hide.
As opposed to a capsule hide (17) (2S-cis-)-3-acetoxy-5-[3-(4-(2-methoxypheny)-1-piperazinyl) propyl]-2, 3-dihydro-2-(4-methoxypheny)-8-chloro -1, 5-benzothiazepine-4 (5H)-ON, Pharmaceutical preparation of 14 above-mentioned publication which contains salts permitted on the medicine manufacture, or those hydrates 40 to 120% of the weight, and contains disintegrator for aminoacetic acid 60 to 90% of the weight one to 20% of the weight.
(18) Pharmaceutical preparation given in either of the above 14-17 whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 45 degree C / sealing is 60% or more.
(19) Pharmaceutical preparation of 18 above-mentioned publication this whose rate of elution is 70% or more.
(20) Pharmaceutical preparation of 18 above-mentioned publication this whose rate of elution is 80% or more.
(21) Pharmaceutical preparation given in either of the above 14-17 whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 45 degree C / sealing is 1.5 or more times as compared with contrast pharmaceutical preparation which does not contain aminoacetic acid.
(22) Pharmaceutical preparation of 17 above-mentioned publication in which a rate of elution

of a publication is shown in the above 21 [0007] Especially as a physic active ingredient which is the chief remedy of this capsule, it is not limited, for example, various antibiotics, an antiviral drug, central-nerves medicine (example: psychopharmaceuticals), deletion nervine, a circulatory system disease remedy (example: a hypotensive agent, heart disease remedy), a antiulcer drug, analgesic, etc. are illustrated. As psychopharmaceuticals, a condensation imidazo pyridine derivative of a publication etc. is illustrated by JP,5-286973,A especially, for example. A compound especially desirable from fields, such as pharmacological activity They are -1, 6 and 7 and 2-(isoxazole-3-IRU) tetrahydroimidazo [9-] [4 and 5-d] PIRANO [4 and 3-b] pyridine given in the example 25, salts permitted on the medicine manufacture, or those hydrates (henceforth [these are named generically and] a compound 1). Moreover, as a circulatory system disease remedy, a benzothiazepine derivative of a publication is illustrated by JP,5-201865,A, for example. An especially desirable compound from fields, such as pharmacological activity, (2S-cis-)-3-acetoxy-5-[3-(4-(2-methoxypheny)-1-piperazinyl) propyl]-2 [given in the example 20], 3-dihydro-2-(4-methoxypheny)-8-chloro -1, They are salts permitted on 5-benzothiazepine-4(5H)-ON and its medicine manufacture, or those hydrates (henceforth [these are named generically and] a compound 2). As a salt permitted on these medicine manufacture, a salt or inner salt formed with an inorganic base, ammonia, an organic base, an inorganic acid, an organic acid, basic amino acid, halogen ion, etc. is illustrated. As this inorganic base, a trimethylamine, triethylamine, a choline, procaine, ethanolamine, etc. are illustrated as alkali metal (Na, K, etc.), alkaline earth metals (calcium, Mg, etc.), and an organic base. As an inorganic acid, a hydrochloric acid, a hydrobromic acid, a sulfuric acid, a nitric acid, a phosphoric acid, etc. are illustrated. As an organic acid, p-toluenesulfonic acid, methansulfonic acid, a formic acid, trifluoroacetic acid, a maleic acid, a citric acid, etc. are illustrated. A lysine, algin, an ornithine, a histidine, etc. are illustrated as a basic amino acid.

[0008] Although what is necessary is just to set up loadings of a physic active ingredient suitably according to the class, an object disease, a patient's condition, etc., they are usually about 5 - 20 % of the weight still more preferably about one to 30% of the weight preferably about 0.1 to 40% of the weight to all capsule weight. To a capsule solid-stowing object, it is about 5 - 30 % of the weight still more preferably about three to 40% of the weight preferably about two to 50% of the weight. To a capsule hide (gelatin), it is about 20 - 85 % of the weight still more preferably about ten to 100% of the weight preferably about five to 150% of the weight. A content ratio of aminoacetic acid is about 2 - 15 % of the weight still more preferably about one to 20% of the weight preferably about 0.5 to 30% of the weight to a capsule hide. Since a content ratio of a chief remedy per capsule falls or evil of insolubilization of a capsule hide fully not being controlled if a content ratio is too low, and it becoming bulky when too high, and enlarging capsule size arises, it makes any and is not desirable. This capsule may contain disintegrator of common use which may usually be used by request in case a ** gelatine capsule agent is prepared, an excipient, a binder, a dissolution assistant, an electrostatic remover, lubricant, a coating agent, an optical stabilizing agent, etc.

[0009] As disintegrator, although partial pregelatinized starch, carboxy-methyl-starch sodium, carboxymethyl-cellulose calcium (CMC calcium), hydroxypropylcellulose (LHPC), crossing carmellose sodium (an example, Ac-Di-Sol, and Asahi Chemical Co., Ltd.), a polyvinyl poly pyrrolidone, etc. are illustrated, for example, they are CMC calcium, LHPC, etc. preferably. A content of disintegrator receives the whole capsule and is usually about 5 - 20 % of the weight preferably [it is desirable and] to about 3 - 40 % of the weight, and a pan about one to 60% of the weight. To a capsule solid-stowing object, it is about 10 - 30 % of the weight still more preferably about five to 50% of the weight preferably about two to 70% of the weight. To a capsule hide, it is about 30 - 90 % of the weight still more preferably about 20 to 95% of the weight preferably about ten to 100% of the weight. As an excipient, although a lactose, white soft sugar, D-mannitol, corn starch, potatostarch, hydroxypropyl starch, etc. are illustrated, for example, there are D-mannitol, corn starch, etc. preferably. A content of an excipient receives the whole capsule and is usually about 35 - 60 % of the weight preferably [it is desirable and] to about 20 - 70 % of the weight, and a pan about ten to 90% of the weight. A

capsule solid–stowing object is received and it is usually about 45 – 80 % of the weight preferably [it is desirable and] to about 40 – 85 % of the weight, and a pan about 30 to 95% of the weight. As a binder, although methyl cellulose, a polyvinyl pyrrolidone, hydroxypropylcellulose (HPC), polyvinyl alcohol, gelatin, a dextrin, etc. are illustrated, for example, it is HPC preferably. A content of a binder is usually about 1 – 5 % of the weight preferably about 0.5 to 10% of the weight to a capsule solid–stowing object. As a dissolution assistant, a succinic acid is illustrated, for example. A content of a dissolution assistant is usually about 1 – 5 % of the weight to a capsule solid–stowing object. As an electrostatic remover, a silica (example: Carplex (Shionogi), Aerosil (Japanese Aerosil, Inc.)) is illustrated. A content of an electrostatic remover is usually about 0.1 – 1 % of the weight to a capsule solid–stowing object.

[0010] As lubricant, magnesium stearate, talc, sucrose fatty acid ester, etc. are illustrated. As a coating agent, polyvinyl–acetal diethylamino acetate, an ethyl–acrylate methacrylic acid methyl copolymer, an aminoalkylmetaacrylatecopolymer, hydroxypropyl–methylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, macro gall, etc. are illustrated. Titanium oxide etc. is illustrated as an optical stabilizing agent. This capsule can be manufactured using the above–mentioned raw material by performing actuation of mixing, kneading, ****, desiccation, refining, ****, encapsulation, etc. according to a well–known method in the field concerned. As a capsule, regular No. 3 or a regular No. 4 capsule is preferably used for a Japanese pharmacopoeia.

[0011] Although a degree of an improvement of chief remedy elution nature in this capsule may be proved by various elution tests, it is shown in an example of the after–mentioned trial by dissolution test of a convention to the 12th amendment Japanese pharmacopoeia etc. like a publication, for example. for example, even when this capsule which contains said compound 1 as a chief remedy is saved for three months under conditions of 40 degrees C / 75% disconnection of relative humidity A rate of elution of the compound 1 20 minutes [by this elution test (conditions: the 2nd law (paddle method), 50rpm, the 2nd liquid (pH 6.8 / about /))] after after test initiation as a desirable mode a chief remedy content in a capsule – – receiving –– at least 60% –– or it is preferably maintainable on 85 – 95% of level especially 70% or more. On the other hand, when contrast pharmaceutical preparation which does not contain aminoacetic acid under these conditions is saved, a rate of elution of the compound 1 of 20 minutes after becomes 40% or less, and falls sharply compared with pharmaceutical preparation of the time of conservation. That is, a compound 1 can improve a rate of elution for example, of 20 minutes after more than twice by combining aminoacetic acid in this capsule. As a desirable mode of this capsule containing a compound 1 As opposed to a capsule hide aminoacetic acid about ten to 50% of the weight for a compound 1 About 1 – 20 % of the weight, Disintegrator is contained about 30 to 60% of the weight. Still more preferably a compound 1 15 – 35 % of the weight, Disintegrator is contained for aminoacetic acid 35 to 55% of the weight three to 15% of the weight, a compound 1 is contained and disintegrator is especially contained for aminoacetic acid 40 to 50% of the weight five to 10% of the weight 20 to 30% of the weight preferably.

[0012] as a mode with a rate of elution of the compound 2 20 minutes after being based on this elution test (conditions: the 2nd law (paddle method), 50rpm, pH4.0 buffer solution) desirable even when this capsule which contains said compound 2 similarly is saved for three months under conditions of 45 degrees C / sealing –– 60% –– or 80 – 90% of level is reached especially preferably 70% or more. On the other hand, when contrast pharmaceutical preparation which does not contain aminoacetic acid under these conditions is saved, a rate of elution of the compound 2 20 minutes after after test initiation becomes about 45%, and falls sharply compared with pharmaceutical preparation of the time of conservation. That is, a compound 2 can improve preferably a rate of elution for example, of 20 minutes after to about 1.8 or more times about 1.5 or more times by combining aminoacetic acid in this capsule. As a desirable mode of this capsule containing a compound 2 As opposed to a capsule hide aminoacetic acid about 60 to 100% of the weight for a compound 2 About 1 – 20 % of the weight, Disintegrator is contained about 60 to 90% of the weight. Still more preferably a

compound 2 About 70 – 90 % of the weight, Disintegrator is contained for aminoacetic acid about 65 to 85% of the weight about one to 15% of the weight, a compound 2 is contained and disintegrator is especially contained for aminoacetic acid 70 to 80% of the weight one to 10% of the weight about 75 to 85% of the weight preferably.

[0013]

[Example] Although the example of this invention is shown below, these do not restrict this invention at all. The following were used as a trial compound.

Compound 1:2– (Isoxazole–3–IRU) 6 –1, 7, 9–[4 and 5–tetrahydroimidazo d] [4 and 3–PIRANO b] pyridine, 1 phosphoric–acid, and 1 hydrate compound 2:(2S–cis–)–3–acetoxy–5–[3–(4–(2–methoxypheny)–1–piperazinyl) propyl]–2 and 3–dihydro–2– All the capsule endocyst components containing (4–methoxypheny)–8–chloro –1, 5–benzothiazepine–4(5H)–ON and 1 citric–acid example 1 (formula) compound 1, aminoacetic acid, etc. were mixed, and the capsule was filled up by the dry type powder filling–up method (henceforth Capsule A). The presentation is shown in a table 1. in addition –– and also it does not blend aminoacetic acid as contrast pharmaceutical preparation –– Capsule A –– the capsule B of the completely same presentation (a No. 4 capsule, a total of 165.0mg) was prepared.

[0014]

[A table 1]

(カプセルA)

成分	含量 (mg)
化合物1	10.0
結晶セルロース PH101	66.2
コーンスターチ	28.38
CMC カルシウム	18.75
カープレックス 67 (シオノギ)	0.42
ステアリン酸Mg	1.25
アミノ酢酸	3.0
4号空カプセル	40.0
合計	168.0

(Elution test) About the above–mentioned capsules A and B, the elution diagram of the compound 1 when saving for three months is shown in drawing 1 and drawing 2 under 40 degrees C and the condition of RH(relative humidity)75% disconnection, respectively.

Test condition: The 12th amendment Japanese pharmacopoeia dissolution test The 2nd law (paddle method) Rotational frequency 50rpm, The rate of elution three months after comparing in early stages of conservation is remarkably delayed by the capsule B which does not add the 2nd liquid (pH about 6.8, temperature of 37 degrees C) (result) aminoacetic acid, and it began to be gradually eluted after 10 minutes, for example, the rate of elution of 20 minutes after was only 35%, and 90% was eluted at last after 60 minutes. On the other hand, by the capsule A which added aminoacetic acid, it began to be eluted after 5 minutes and 91% of rate of elution was reached after 20 minutes. That is, it turned out that insolubilization of a ** gelatine capsule agent is notably controlled by addition of aminoacetic acid, and the rate of elution is improved.

[0015] Wet agglomeration, after drying and refining, when ****(ing) magnesium stearate in a hydroxypropylcellulose (HPC SL) aqueous solution for example 2 (formula) compound 2, hydroxypropylcellulose (LHPC31), D–mannitol, and a succinic acid, aminoacetic acid was also mixed to coincidence and the capsule was filled up (capsule C). The presentation is shown in a table 2. in addition –– and also it does not blend aminoacetic acid as contrast pharmaceutical preparation –– Capsule C –– the capsule D of the completely same presentation (a No. 3 capsule, a total of 230.0mg) was prepared.

[0016]

[A table 2]

(カプセルC)

成分	含量 (mg)
化合物2	40.0
LHPC31	36.6
D-マンニトール	92.2
コハク酸	5.0
HPC SL (液添加)	5.0
アミノ酢酸 (外添加)	2.0
ステアリン酸Mg (外添加)	1.8
3号空カプセル	50.0
合計	232.0

(Elution test) About the above-mentioned capsules C and D, it is 45 degrees C. Sealing The elution diagram of the compound 2 when saving for three months is shown in drawing 3 and drawing 4 under a condition, respectively.
Test condition: The 12th amendment Japanese pharmacopoeia dissolution test The 2nd law (paddle method) The rate of elution three months after comparing in early stages of conservation is remarkably delayed by the capsule D which does not add rotational frequency 50rpm and acetic-acid buffer-solution (pH4.0, temperature of 37 degrees C) (result) aminoacetic acid, and it began to be gradually eluted after 5 minutes, for example, the rate of elution of 20 minutes after was only 43%, and did not reach to 80% after 60 minutes. On the other hand, by the capsule C which added aminoacetic acid, it began to be immediately eluted after test initiation, and 84% of rate of elution was already reached after 20 minutes. That is, it turned out that insolubilization of a ** gelatine capsule is notably controlled by addition of aminoacetic acid, and the rate of elution is improved.
[0017]
[Effect of the Invention] Even if insolubilization of a capsule hide is controlled and it carries out the mothball of this capsule under warming and humidification conditions by containing aminoacetic acid, there is little aging of the capsule itself, and remarkable elution delay of an endocyst drug is not accepted. Moreover, even if itself is water-soluble very stable and high material compared with a high polymer like protein and it carries out the endocyst of the aminoacetic acid to a capsule, we are not anxious about the bad influence to a pharmaceutical preparation property.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

TECHNICAL FIELD

[A technical field to which invention belongs] This invention relates to a ** gelatine capsule agent by which the elution nature of a chief remedy has been improved.

[Translation done.]

* NOTICES *

PRIOR ART

[Description of the Prior Art] A ** gelatine capsule agent has the trouble that gelatin starts and insolubilizes aging, such as bridge formation and a polymerization, between intramolecular or a molecule, consequently the emission nature of an endocyst drug is delayed remarkably in the mothball middle class, when the amino group in the gelatin which is a capsule hide causes amino-carbonyl reactions, such as reducing sugar in packing, other aldehydes, and a Maillard reaction. As a means to solve such a problem conventionally, the method of blending various kinds of protein, amino acid, the material of amino-group content, or an anti-oxidant into an encapsulation object is indicated by JP,49-599817,A, and aminoacetic acid (glycine) is also indicated as an example of amino acid. However, the example of the ** gelatine capsule agent which blended aminoacetic acid is not indicated. Moreover, the method of blending a free radical trapping agent into an encapsulation object is indicated as a means to prevent insolubilization of a ** gelatine capsule agent by JP,8-99869,A. This technology is not the means which prevents generating of the free radical used as the generation source of peroxides, such as aldehydes, and carries out direct inhibition of the above amino-carbonyl reaction itself by the free radical trapping agent. Moreover, aminoacetic acid is not indicated as an example of a free radical trapping agent.

[Translation done.]

* NOTICES *

EFFECT OF THE INVENTION

[Effect of the Invention] Even if insolubilization of a capsule hide is controlled and it carries out the mothball of this capsule under warming and humidification conditions by containing aminoacetic acid, there is little aging of the capsule itself, and remarkable elution delay of an endocyst drug is not accepted. Moreover, even if itself is water-soluble very stable and high material compared with a high polymer like protein and it carries out the endocyst of the aminoacetic acid to a capsule, we are not anxious about the bad influence to a pharmaceutical preparation property.

[Translation done.]

* NOTICES *

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] Insolubilization of gelatin was controlled and development of the new ** gelatine capsule agent by which the elution nature of a chief remedy has been improved was demanded.

[Translation done.]

* NOTICES *

MEANS

[Means for Solving the Problem] When making aminoacetic acid live together in packing of a ** gelatine capsule agent as a result of this invention persons' inquiring wholeheartedly in view of the above-mentioned technical problem, this invention which shows that insolubilization of gelatin is controlled and the elution nature of a chief remedy is improved to a header and the following was completed.
(1) A ** gelatine capsule agent which is characterized by containing aminoacetic acid in an encapsulation object and by which elution nature has been improved (henceforth this capsule).
(2) Pharmaceutical preparation of one above-mentioned publication which contains aminoacetic acid 0.5 to 30% of the weight to a capsule hide.
(3) Pharmaceutical preparation of the above 1 or 2 publications which contain a condensation imidazo pyridine derivative as a physic active ingredient.
(4) Pharmaceutical preparation of three above-mentioned publication whose condensation imidazo pyridine derivatives are -1, 6 and 7, 2-(isoxazole-3-IRU) tetrahydroimidazo [9-] [4 and 5-d] PIRANO [4 and 3-b] pyridine, salts permitted on the medicine manufacture, or those hydrates.
(5) Pharmaceutical preparation of four above-mentioned publication which contains aminoacetic acid one to 20% of the weight to a capsule hide.
(6) Pharmaceutical preparation of the above-mentioned 5 ** which contain disintegrator 30 to 60% of the weight to a capsule hide.
(7) Pharmaceutical preparation of four above-mentioned publication which contains -1, 6 and 7, 2-(isoxazole-3-IRU) tetrahydroimidazo [9-] [4 and 5-d] PIRANO [4 and 3-b] pyridine, salts permitted on the medicine manufacture, or those hydrates ten to 50% of the weight to a capsule hide, and contains disintegrator for aminoacetic acid 30 to 60% of the weight one to 20% of the weight.
(8) Pharmaceutical preparation according to claim 4 to 7 whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 40 degree C / 75% disconnection of relative humidity is 60% or more.
[0005] (9) Pharmaceutical preparation of eight above-mentioned publication this whose rate of elution is 70% or more.
(10) Pharmaceutical preparation of eight above-mentioned publication this whose rate of elution is 80% or more.
(11) Pharmaceutical preparation given in either of the above 4-7 it is twice [more than] whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 40 degree C / 75% disconnection of relative humidity of this as compared with contrast pharmaceutical preparation which does not contain aminoacetic acid.
(12) Pharmaceutical preparation given in the above 7 which shows a rate of elution of a publication to the above 11.
(13) Pharmaceutical preparation given in the above 1 or 2 which contains a benzothiazepine

derivative as a physic active ingredient.
(14) Pharmaceutical preparation of 13 above-mentioned publication whose benzothiazepine derivatives are salts permitted on (2S-cis-)-3-acetoxy-5-[3-(4-(2-methoxypheny)-1-piperazinyl) propyl]-2, 3-dihydro-2-(4-methoxypheny)-8-chloro -1, 5-benzothiazepine-4 (5H)-ON, and its medicine manufacture, or those hydrates.
(15) Pharmaceutical preparation of 14 above-mentioned publication which contains aminoacetic acid one to 20% of the weight to a capsule hide.
[0006] (16) Pharmaceutical preparation of 15 above-mentioned publication which contains disintegrator 60 to 90% of the weight to a capsule hide.
As opposed to a capsule hide (17) (2S-cis-)-3-acetoxy-5-[3-(4-(2-methoxypheny)-1-piperazinyl) propyl]-2, 3-dihydro-2-(4-methoxypheny)-8-chloro -1, 5-benzothiazepine-4 (5H)-ON, Pharmaceutical preparation of 14 above-mentioned publication which contains salts permitted on the medicine manufacture, or those hydrates 40 to 120% of the weight, and contains disintegrator for aminoacetic acid 60 to 90% of the weight one to 20% of the weight.
(18) Pharmaceutical preparation given in either of the above 14-17 whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 45 degree C / sealing is 60% or more.
(19) Pharmaceutical preparation of 18 above-mentioned publication this whose rate of elution is 70% or more.
(20) Pharmaceutical preparation of 18 above-mentioned publication this whose rate of elution is 80% or more.
(21) Pharmaceutical preparation given in either of the above 14-17 whose rate of elution of a physic active ingredient 20 minutes after being based on a dissolution test (the 2nd law, paddle method) of a convention to the 12th amendment Japanese pharmacopoeia at the time of saving for three months under conditions of 45 degree C / sealing is 1.5 or more times as compared with contrast pharmaceutical preparation which does not contain aminoacetic acid.
(22) Pharmaceutical preparation of 17 above-mentioned publication in which a rate of elution of a publication is shown in the above 21 [0007] Especially as a physic active ingredient which is the chief remedy of this capsule, it is not limited, for example, various antibiotics, an antiviral drug, central-nerves medicine (example: psychopharmaceuticals), deletion nervine, a circulatory system disease remedy (example: a hypotensive agent, heart disease remedy), a antiulcer drug, analgesic, etc. are illustrated. As psychopharmaceuticals, a condensation imidazo pyridine derivative of a publication etc. is illustrated by JP,5-286973,A especially, for example. A compound especially desirable from fields, such as pharmacological activity They are -1, 6 and 7 and 2-(isoxazole-3-IRU) tetrahydroimidazo [9-] [4 and 5-d] PIRANO [4 and 3-b] pyridine given in the example 25, salts permitted on the medicine manufacture, or those hydrates (henceforth [these are named generically and] a compound 1). Moreover, as a circulatory system disease remedy, a benzothiazepine derivative of a publication is illustrated by JP,5-201865,A, for example. An especially desirable compound from fields, such as pharmacological activity, (2S-cis-)-3-acetoxy-5-[3-(4-(2-methoxypheny)-1-piperazinyl) propyl]-2 [given in the example 20], 3-dihydro-2-(4-methoxypheny)-8-chloro -1, They are salts permitted on 5-benzothiazepine-4(5H)-ON and its medicine manufacture, or those hydrates (henceforth [these are named generically and] a compound 2). As a salt permitted on these medicine manufacture, a salt or inner salt formed with an inorganic base, ammonia, an organic base, an inorganic acid, an organic acid, basic amino acid, halogen ion, etc. is illustrated. As this inorganic base, a trimethylamine, triethylamine, a choline, procaine, ethanolamine, etc. are illustrated as alkali metal (Na, K, etc.), alkaline earth metals (calcium, Mg, etc.), and an organic base. As an inorganic acid, a hydrochloric acid, a hydrobromic acid, a sulfuric acid, a nitric acid, a phosphoric acid, etc. are illustrated. As an organic acid, p-toluenesulfonic acid, methansulfonic acid, a formic acid, trifluoroacetic acid, a maleic acid, a citric acid, etc. are illustrated. A lysine, algin, an ornithine, a histidine, etc. are illustrated as a basic amino acid.
[0008] Although what is necessary is just to set up loadings of a physic active ingredient

suitably according to the class, an object disease, a patient's condition, etc., they are usually about 5 − 20 % of the weight still more preferably about one to 30% of the weight preferably about 0.1 to 40% of the weight to all capsule weight. To a capsule solid−stowing object, it is about 5 − 30 % of the weight still more preferably about three to 40% of the weight preferably about two to 50% of the weight. To a capsule hide (gelatin), it is about 20 − 85 % of the weight still more preferably about ten to 100% of the weight preferably about five to 150% of the weight. A content ratio of aminoacetic acid is about 2 − 15 % of the weight still more preferably about one to 20% of the weight preferably about 0.5 to 30% of the weight to a capsule hide. Since a content ratio of a chief remedy per capsule falls or evil of insolubilization of a capsule hide fully not being controlled if a content ratio is too low, and it becoming bulky when too high, and enlarging capsule size arises, it makes any and is not desirable. This capsule may contain disintegrator of common use which may usually be used by request in case a ** gelatine capsule agent is prepared, an excipient, a binder, a dissolution assistant, an electrostatic remover, lubricant, a coating agent, an optical stabilizing agent, etc.
[0009] As disintegrator, although partial pregelatinized starch, carboxy−methyl−starch sodium, carboxymethyl−cellulose calcium (CMC calcium), hydroxypropylcellulose (LHPC), crossing carmellose sodium (an example, Ac−Di−Sol, and Asahi Chemical Co., Ltd.), a polyvinyl poly pyrrolidone, etc. are illustrated, for example, they are CMC calcium, LHPC, etc. preferably. A content of disintegrator receives the whole capsule and is usually about 5 − 20 % of the weight preferably [it is desirable and] to about 3 − 40 % of the weight, and a pan about one to 60% of the weight. To a capsule solid−stowing object, it is about 10 − 30 % of the weight still more preferably about five to 50% of the weight preferably about two to 70% of the weight. To a capsule hide, it is about 30 − 90 % of the weight still more preferably about 20 to 95% of the weight preferably about ten to 100% of the weight. As an excipient, although a lactose, white soft sugar, D−mannitol, corn starch, potatostarch, hydroxypropyl starch, etc. are illustrated, for example, there are D−mannitol, corn starch, etc. preferably. A content of an excipient receives the whole capsule and is usually about 35 − 60 % of the weight preferably [it is desirable and] to about 20 − 70 % of the weight, and a pan about ten to 90% of the weight. A capsule solid−stowing object is received and it is usually about 45 − 80 % of the weight preferably [it is desirable and] to about 40 − 85 % of the weight, and a pan about 30 to 95% of the weight. As a binder, although methyl cellulose, a polyvinyl pyrrolidone, hydroxypropylcellulose (HPC), polyvinyl alcohol, gelatin, a dextrin, etc. are illustrated, for example, it is HPC preferably. A content of a binder is usually about 1 − 5 % of the weight preferably about 0.5 to 10% of the weight to a capsule solid−stowing object. As a dissolution assistant, a succinic acid is illustrated, for example. A content of a dissolution assistant is usually about 1 − 5 % of the weight to a capsule solid−stowing object. As an electrostatic remover, a silica (example: Carplex (Shionogi), Aerosil (Japanese Aerosil, Inc.)) is illustrated. A content of an electrostatic remover is usually about 0.1 − 1 % of the weight to a capsule solid−stowing object.
[0010] As lubricant, magnesium stearate, talc, sucrose fatty acid ester, etc. are illustrated. As a coating agent, polyvinyl−acetal diethylamino acetate, an ethyl−acrylate methacrylic acid methyl copolymer, an aminoalkylmetaacrylatecopolymer, hydroxypropyl−methylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, macro gall, etc. are illustrated. Titanium oxide etc. is illustrated as an optical stabilizing agent. This capsule can be manufactured using the above−mentioned raw material by performing actuation of mixing, kneading, ****, desiccation, refining, ****, encapsulation, etc. according to a well−known method in the field concerned. As a capsule, regular No. 3 or a regular No. 4 capsule is preferably used for a Japanese pharmacopoeia.
[0011] Although a degree of an improvement of chief remedy elution nature in this capsule may be proved by various elution tests, it is shown in an example of the after−mentioned trial by dissolution test of a convention to the 12th amendment Japanese pharmacopoeia etc. like a publication, for example. for example, even when this capsule which contains said compound 1 as a chief remedy is saved for three months under conditions of 40 degrees C / 75% disconnection of relative humidity A rate of elution of the compound 1 20 minutes [by this

elution test (conditions: the 2nd law (paddle method), 50rpm, the 2nd liquid (pH 6.8 / about /))] after after test initiation as a desirable mode a chief remedy content in a capsule — — receiving —— at least 60% —— or it is preferably maintainable on 85 — 95% of level especially 70% or more. On the other hand, when contrast pharmaceutical preparation which does not contain aminoacetic acid under these conditions is saved, a rate of elution of the compound 1 of 20 minutes after becomes 40% or less, and falls sharply compared with pharmaceutical preparation of the time of conservation. That is, a compound 1 can improve a rate of elution for example, of 20 minutes after more than twice by combining aminoacetic acid in this capsule. As a desirable mode of this capsule containing a compound 1 As opposed to a capsule hide aminoacetic acid about ten to 50% of the weight for a compound 1 About 1 — 20 % of the weight, Disintegrator is contained about 30 to 60% of the weight. Still more preferably a compound 1 15 — 35 % of the weight, Disintegrator is contained for aminoacetic acid 35 to 55% of the weight three to 15% of the weight, a compound 1 is contained and disintegrator is especially contained for aminoacetic acid 40 to 50% of the weight five to 10% of the weight 20 to 30% of the weight preferably.

[0012] as a mode with a rate of elution of the compound 2 20 minutes after being based on this elution test (conditions: the 2nd law (paddle method), 50rpm, pH4.0 buffer solution) desirable even when this capsule which contains said compound 2 similarly is saved for three months under conditions of 45 degrees C / sealing —— 60% —— or 80 — 90% of level is reached especially preferably 70% or more. On the other hand, when contrast pharmaceutical preparation which does not contain aminoacetic acid under these conditions is saved, a rate of elution of the compound 2 20 minutes after after test initiation becomes about 45%, and falls sharply compared with pharmaceutical preparation of the time of conservation. That is, a compound 2 can improve preferably a rate of elution for example, of 20 minutes after to about 1.8 or more times about 1.5 or more times by combining aminoacetic acid in this capsule. As a desirable mode of this capsule containing a compound 2 As opposed to a capsule hide aminoacetic acid about 60 to 100% of the weight for a compound 2 About 1 — 20 % of the weight, Disintegrator is contained about 60 to 90% of the weight. Still more preferably a compound 2 About 70 — 90 % of the weight, Disintegrator is contained for aminoacetic acid about 65 to 85% of the weight about one to 15% of the weight, a compound 2 is contained and disintegrator is especially contained for aminoacetic acid 70 to 80% of the weight one to 10% of the weight about 75 to 85% of the weight preferably.

[Translation done.]

* NOTICES *

EXAMPLE

[Example] Although the example of this invention is shown below, these do not restrict this invention at all. The following were used as a trial compound.
Compound 1:2- (Isoxazole-3-IRU) 6 -1, 7, 9-[4 and 5-tetrahydroimidazo d] [4 and 3-PIRANO b] pyridine, 1 phosphoric-acid, and 1 hydrate compound 2:(2S-cis-)-3-acetoxy-5-[3-(4-(2-methoxypheny)-1-piperazinyl) propyl]-2 and 3-dihydro-2- All the capsule endocyst components containing (4-methoxypheny)-8-chloro -1, 5-benzothiazepine-4(5H)-ON and 1 citric-acid example 1 (formula) compound 1, aminoacetic acid, etc. were mixed, and the capsule was filled up by the dry type powder filling-up method (henceforth Capsule A). The presentation is shown in a table 1. in addition -- and also it does not blend aminoacetic acid as contrast pharmaceutical preparation -- Capsule A -- the capsule B of the completely same presentation (a No. 4 capsule, a total of 165.0mg) was prepared.
[0014]
[A table 1]
(カプセルA)

成分	含量 (mg)
化合物1	10.0
結晶セルロース PH101	66.2
コーンスターチ	28.38
CMCカルシウム	18.75
カープレックス67 (シオノギ)	0.42
ステアリン酸Mg	1.25
アミノ酢酸	3.0
4号空カプセル	40.0
合計	168.0

(Elution test) About the above-mentioned capsules A and B, the elution diagram of the compound 1 when saving for three months is shown in drawing 1 and drawing 2 under 40 degrees C and the condition of RH(relative humidity)75% disconnection, respectively.
Test condition: The 12th amendment Japanese pharmacopoeia dissolution test The 2nd law (paddle method) Rotational frequency 50rpm, The rate of elution three months after comparing in early stages of conservation is remarkably delayed by the capsule B which does not add the 2nd liquid (pH about 6.8, temperature of 37 degrees C) (result) aminoacetic acid, and it began to be gradually eluted after 10 minutes, for example, the rate of elution of 20 minutes after was only 35%, and 90% was eluted at last after 60 minutes. On the other hand, by the capsule A which added aminoacetic acid, it began to be eluted after 5 minutes and 91% of rate of elution was reached after 20 minutes. That is, it turned out that insolubilization of a ** gelatine capsule agent is notably controlled by addition of aminoacetic acid, and the rate of elution is improved.
[0015] Wet agglomeration, after drying and refining, when ****(ing) magnesium stearate in a hydroxypropylcellulose (HPC SL) aqueous solution for example 2 (formula) compound 2, hydroxypropylcellulose (LHPC31), D-mannitol, and a succinic acid, aminoacetic acid was also mixed to coincidence and the capsule was filled up (capsule C). The presentation is shown in a table 2. in addition -- and also it does not blend aminoacetic acid as contrast pharmaceutical preparation -- Capsule C -- the capsule D of the completely same presentation (a No. 3 capsule, a total of 230.0mg) was prepared.

[0016]
[A table 2]
(カプセルC)

成分	含量 (mg)
化合物2	40.0
LHPC31	36.6
D-マンニトール	92.2
コハク酸	5.0
HPC SL (液添加)	5.0
アミノ酢酸 (外添加)	2.0
ステアリン酸Mg (外添加)	1.8
3号空カプセル	50.0
合計	232.0

(Elution test) About the above-mentioned capsules C and D, it is 45 degrees C. Sealing The elution diagram of the compound 2 when saving for three months is shown in drawing 3 and drawing 4 under a condition, respectively.
Test condition: The 12th amendment Japanese pharmacopoeia dissolution test The 2nd law (paddle method) The rate of elution three months after comparing in early stages of conservation is remarkably delayed by the capsule D which does not add rotational frequency 50rpm and acetic-acid buffer-solution (pH4.0, temperature of 37 degrees C) (result) aminoacetic acid, and it began to be gradually eluted after 5 minutes, for example, the rate of elution of 20 minutes after was only 43%, and did not reach to 80% after 60 minutes. On the other hand, by the capsule C which added aminoacetic acid, it began to be immediately eluted after test initiation, and 84% of rate of elution was already reached after 20 minutes. That is, it turned out that insolubilization of a ** gelatine capsule is notably controlled by addition of aminoacetic acid, and the rate of elution is improved.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DESCRIPTION OF DRAWINGS

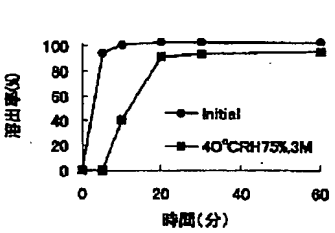
[Brief Description of the Drawings]
[Drawing 1] It is the graph which shows aging of the elution nature of a chief remedy about the ** gelatine capsule agent of the compound 1 containing aminoacetic acid.
[Drawing 2] It is the graph which shows aging of the elution nature of a chief remedy about the ** gelatine capsule agent of the compound 1 which does not contain aminoacetic acid.
[Drawing 3] It is the graph which shows aging of the elution nature of a chief remedy about the ** gelatine capsule agent of the compound 2 containing aminoacetic acid.
[Drawing 4] It is the graph which shows aging of the elution nature of a chief remedy about the ** gelatine capsule agent of the compound 2 which does not contain aminoacetic acid.

[Translation done.]

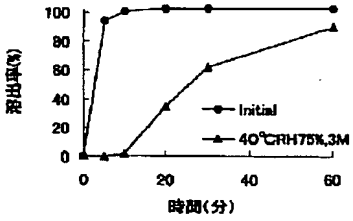
* NOTICES *

DRAWINGS

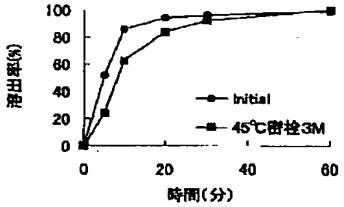
[Drawing 1]



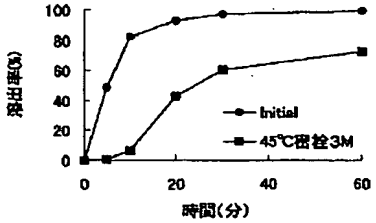
[Drawing 2]



[Drawing 3]



[Drawing 4]



[Translation done.]

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最終頁に続く

(54)【発明の名称】　溶出性が改善された硬ゼラチンカプセル剤

(57)【要約】
【課題】硬ゼラチンカプセル剤におけるカプセル剤皮の不溶化、およびそれに伴う主薬の溶出遅延を抑制する。
【解決手段】カプセル充填物中にアミノ酢酸を含有することを特徴とする、カプセル剤皮の不溶化が抑制された硬ゼラチンカプセル剤。

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【特許請求の範囲】
【請求項１】カプセル充填物中にアミノ酢酸を含有することを特徴とする、溶出性が改善された硬ゼラチンカプセル剤。
【請求項２】カプセル剤皮に対してアミノ酢酸を０．５～３０重量％含有する、請求項１記載の製剤。
【請求項３】医薬活性成分として縮合イミダゾピリジン誘導体を含有する、請求項１または２記載の製剤。
【請求項４】縮合イミダゾピリジン誘導体が、２－（イソオキサゾール－３－イル）－１，６，７，９－テトラヒドロイミダゾ[４，５－ｄ]ピラノ[４，３－ｂ]ピリジン、その製薬上許容される塩、またはそれらの水和物である、請求項３記載の製剤。
【請求項５】カプセル剤皮に対してアミノ酢酸を１～２０重量％含有する、請求項４記載の製剤。
【請求項６】カプセル剤皮に対して崩壊剤を３０～６０重量％含有する、請求項５載の製剤。
【請求項７】カプセル剤皮に対して、２－（イソオキサゾール－３－イル）－１，６，７，９－テトラヒドロイミダゾ[４，５－ｄ]ピラノ[４，３－ｂ]ピリジン、その製薬上許容される塩、またはそれらの水和物を１０～５０重量％、アミノ酢酸を１～２０重量％、崩壊剤を３０～６０重量％含有する、請求項４記載の製剤。
【請求項８】４０℃／相対湿度７５％開放の条件下で３ケ月間保存した場合の第１２改正日本薬局方に規定の溶出試験法（第２法，パドル法）による２０分後の医薬活性成分の溶出率が、６０％以上である、請求項４～７のいずれかに記載の製剤。
【請求項９】該溶出率が７０％以上である、請求項８記載の製剤。
【請求項１０】該溶出率が８０％以上である、請求項８記載の製剤。
【請求項１１】４０℃／相対湿度７５％開放の条件下で３ケ月間保存した場合の第１２改正日本薬局方に規定の溶出試験法（第２法，パドル法）による２０分後の医薬活性成分の溶出率が、アミノ酢酸を含有しない対照製剤と比較して２倍以上である、請求項４～７のいずれかに記載の製剤。
【請求項１２】請求項１１に記載の溶出率を示す、請求項７に記載の製剤。
【請求項１３】医薬活性成分としてベンゾチアゼピン誘導体を含有する、請求項１または２に記載の製剤。
【請求項１４】ベンゾチアゼピン誘導体が、（２Ｓ－シス）－３－アセトキシ－５－[３－（４－（２－メトキシフェニル）－１－ピペラジニル）プロピル]－２，３－ジヒドロ－２－（４－メトキシフェニル）－８－クロロ－１，５－ベンゾチアゼピン－４（５Ｈ）－オン、その製薬上許容される塩、またはそれらの水和物である、請求項１３記載の製剤。
【請求項１５】カプセル剤皮に対してアミノ酢酸を１～

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２０重量％含有する、請求項１４記載の製剤。
【請求項１６】カプセル剤皮に対して崩壊剤を６０～９０重量％含有する、請求項１５記載の製剤。
【請求項１７】カプセル剤皮に対して、（２Ｓ－シス）－３－アセトキシ－５－[３－（４－（２－メトキシフェニル）－１－ピペラジニル）プロピル]－２，３－ジヒドロ－２－（４－メトキシフェニル）－８－クロロ－１，５－ベンゾチアゼピン－４（５Ｈ）－オン、その製薬上許容される塩、またはそれらの水和物を６０～１００重量％、アミノ酢酸を１～２０重量％、崩壊剤を６０～９０重量％含有する、請求項１４記載の製剤。
【請求項１８】４５℃／密栓の条件下で３ケ月間保存した場合の、第１２改正日本薬局方に規定の溶出試験法（第２法，パドル法）による２０分後の医薬活性成分の溶出率が、６０％以上である、請求項１４～１７のいずれかに記載の製剤。
【請求項１９】該溶出率が７０％以上である、請求項１８記載の製剤。
【請求項２０】該溶出率が８０％以上である、請求項１８記載の製剤。
【請求項２１】４５℃／密栓の条件下で３ケ月間保存した場合の、第１２改正日本薬局方に規定の溶出試験法（第２法，パドル法）による２０分後の医薬活性成分の溶出率が、アミノ酢酸を含有しない対照製剤と比較して1.５倍以上である、請求項１４～１７のいずれかに記載の製剤。
【請求項２２】請求項２１に記載の溶出率を示す、請求項１７記載の製剤
【発明の詳細な説明】
【０００１】
【発明が属する技術分野】本発明は、主薬の溶出性が改善された硬ゼラチンカプセル剤に関する。
【０００２】
【従来の技術】硬ゼラチンカプセル剤は、長期保存中等に、カプセル剤皮であるゼラチン中のアミノ基が、充填物中の還元糖やその他のアルデヒド類等とメイラード反応等のアミノカルボニル反応をおこすことによって、ゼラチンが分子内または分子間で架橋や重合等の経時変化をおこして不溶化し、その結果、内包薬物の放出性が著しく遅延する問題点がある。従来、このような問題を解決する手段として、例えば特開昭４９－５９９８１７には、カプセル充填物中に各種の蛋白質類、アミノ酸類、アミノ基含有の物質、または抗酸化剤等を配合する方法が開示されており、アミノ酸類の一例としてアミノ酢酸（グリシン）も記載されている。しかし、アミノ酢酸を配合した硬ゼラチンカプセル剤の具体例は記載されていない。また特開平８－９９８６９には、硬ゼラチンカプセル剤の不溶化を防止する手段として、カプセル充填物中にフリーラジカル捕獲剤を配合する方法が開示されている。この技術は、フリーラジカル捕獲剤によって、ア

ルデヒド類等の過酸化物の発生源となるフリーラジカルの発生を防止するものであり、前記のアミノカルボニル反応自体を直接抑制する手段ではない。またフリーラジカル捕獲剤の具体例として、アミノ酢酸は記載されていない。

【０００３】

【発明が解決しようとする課題】ゼラチンの不溶化が抑制されて、主薬の溶出性が改善された新規な硬ゼラチンカプセル剤の開発が要望されていた。

【０００４】

【課題を解決するための手段】上記課題に鑑み本発明者らは鋭意検討した結果、硬ゼラチンカプセル剤の充填物中にアミノ酢酸を共存させれば、ゼラチンの不溶化が抑制されて主薬の溶出性が改善されることを見出し、以下に示す本発明を完成した。

（１）カプセル充填物中にアミノ酢酸を含有することを特徴とする、溶出性が改善された硬ゼラチンカプセル剤（以下、本カプセル剤ともいう）。

（２）カプセル剤皮に対してアミノ酢酸を０．５～３０重量％含有する、上記１記載の製剤。

（３）医薬活性成分として縮合イミダゾピリジン誘導体を含有する、上記１または２記載の製剤。

（４）縮合イミダゾピリジン誘導体が、２－（イソオキサゾール－３－イル）－１，６，７，９－テトラヒドロイミダゾ[４，５－ｄ]ピラノ[４，３－ｂ]ピリジン、その製薬上許容される塩、またはそれらの水和物である、上記３記載の製剤。

（５）カプセル剤皮に対してアミノ酢酸を１～２０重量％含有する、上記４記載の製剤。

（６）カプセル剤皮に対して崩壊剤を３０～６０重量％含有する、上記５載の製剤。

（７）カプセル剤皮に対して、２－（イソオキサゾール－３－イル）－１，６，７，９－テトラヒドロイミダゾ[４，５－ｄ]ピラノ[４，３－ｂ]ピリジン、その製薬上許容される塩、またはそれらの水和物を１０～５０重量％、アミノ酢酸を１～２０重量％、崩壊剤を３０～６０重量％含有する、上記４記載の製剤。

（８）４０℃／相対湿度７５％開放の条件下で３ケ月間保存した場合の第１２改正日本薬局方に規定の溶出試験法（第２法，パドル法）による２０分後の医薬活性成分の溶出率が、６０％以上である、請求項４～７のいずれかに記載の製剤。

【０００５】（９）該溶出率が７０％以上である、上記８記載の製剤。

（１０）該溶出率が８０％以上である、上記８記載の製剤。

（１１）４０℃／相対湿度７５％開放の条件下で３ケ月間保存した場合の第１２改正日本薬局方に規定の溶出試験法（第２法，パドル法）による２０分後の医薬活性成分の溶出率が、アミノ酢酸を含有しない対照製剤と比較して２倍以上である、上記４～７のいずれかに記載の製剤。

（１２）上記１１に記載の溶出率を示す、上記７に記載の製剤。

（１３）医薬活性成分としてベンゾチアゼピン誘導体を含有する、上記１または２に記載の製剤。

（１４）ベンゾチアゼピン誘導体が、（２Ｓ－シス）－３－アセトキシ－５－[３－（４－（２－メトキシフェニル）－１－ピペラジニル）プロピル]－２，３－ジヒドロ－２－（４－メトキシフェニル）－８－クロロ－１，５－ベンゾチアゼピン－４（５Ｈ）－オン、その製薬上許容される塩、またはそれらの水和物である、上記１３記載の製剤。

（１５）カプセル剤皮に対してアミノ酢酸を１～２０重量％含有する、上記１４記載の製剤。

【０００６】（１６）カプセル剤皮に対して崩壊剤を６０～９０重量％含有する、上記１５記載の製剤。

（１７）カプセル剤皮に対して、（２Ｓ－シス）－３－アセトキシ－５－[３－（４－（２－メトキシフェニル）－１－ピペラジニル）プロピル]－２，３－ジヒドロ－２－（４－メトキシフェニル）－８－クロロ－１，５－ベンゾチアゼピン－４（５Ｈ）－オン、その製薬上許容される塩、またはそれらの水和物を４０～１２０重量％、アミノ酢酸を１～２０重量％、崩壊剤を６０～９０重量％含有する、上記１４記載の製剤。

（１８）４５℃／密栓の条件下で３ケ月間保存した場合の、第１２改正日本薬局方に規定の溶出試験法（第２法，パドル法）による２０分後の医薬活性成分の溶出率が、６０％以上である、上記１４～１７のいずれかに記載の製剤。

（１９）該溶出率が７０％以上である、上記１８記載の製剤。

（２０）該溶出率が８０％以上である、上記１８記載の製剤。

（２１）４５℃／密栓の条件下で３ケ月間保存した場合の、第１２改正日本薬局方に規定の溶出試験法（第２法，パドル法）による２０分後の医薬活性成分の溶出率が、アミノ酢酸を含有しない対照製剤と比較して1.５倍以上である、上記１４～１７のいずれかに記載の製剤。

（２２）上記２１に記載の溶出率を示す、上記１７記載の製剤

【０００７】本カプセル剤の主薬である医薬活性成分としては、特に限定されず、例えば種々の抗生物質、抗ウイルス薬、中枢神経薬（例：抗精神薬）、抹消神経薬、循環器系疾患治療薬（例：降圧薬、心疾患治療薬）、抗潰瘍薬、鎮痛薬等が例示される。中でも抗精神薬としては、例えば特開平５－２８６９７３に記載の縮合イミダゾピリジン誘導体等が例示され、とりわけ薬理活性等の面から好ましい化合物は、その実施例２５に記載の２－（イソオキサゾール－３－イル）－１，６，７，９－テト

ラヒドロイミダゾ[４，５－ｄ]ピラノ[４，３－ｂ]ピリジン、その製薬上許容される塩、またはそれらの水和物（以下、これらを総称して化合物１ともいう）である。また循環器系疾患治療薬としては、例えば特開平５－２０１８６５に記載のベンゾチアゼピン誘導体が例示され、とりわけ薬理活性等の面から好ましい化合物はその実施例２０に記載の（２Ｓ－シス）－３－アセトキシ－５－[３－（４－（２－メトキシフェニル）－１－ピペラジニル）プロピル]－２，３－ジヒドロ－２－（４－メトキシフェニル）－８－クロロ－１，５－ベンゾチアゼピン－４（５Ｈ）－オン、その製薬上許容される塩、またはそれらの水和物（以下、これらを総称して化合物２ともいう）である。これらの製薬上許容される塩としては、無機塩基、アンモニア、有機塩基、無機酸、有機酸、塩基性アミノ酸、ハロゲンイオン等により形成される塩又は分子内塩が例示される。該無機塩基としては、アルカリ金属（Ｎａ，Ｋ等）、アルカリ土類金属（Ｃａ，Ｍｇ等）、有機塩基としては、トリメチルアミン、トリエチルアミン、コリン、プロカイン、エタノールアミン等が例示される。無機酸としては、塩酸、臭化水素酸、硫酸、硝酸、リン酸等が例示される。有機酸としては、ｐ－トルエンスルホン酸、メタンスルホン酸、ギ酸、トリフルオロ酢酸、マレイン酸、クエン酸等が例示される。塩基性アミノ酸としては、リジン、アルギン、オルニチン、ヒスチジン等が例示される。

【０００８】医薬活性成分の配合量は、その種類、対象疾患、患者の状態等に応じて、適宜設定すればよいが、通常、カプセル剤全重量に対して約０．１～４０重量％、好ましくは約１～３０重量％、さらに好ましくは約５～２０重量％である。カプセル全充填物に対しては、約２～５０重量％、好ましくは約３～４０重量％、さらに好ましくは約５～３０重量％である。カプセル剤皮（ゼラチン）に対しては、約５～１５０重量％、好ましくは約１０～１００重量％、さらに好ましくは約２０～８５重量％である。アミノ酢酸の含有比は、カプセル剤皮に対して約０．５～３０重量％、好ましくは約１～２０重量％、さらに好ましくは約２～１５重量％である。含有比が低すぎるとカプセル剤皮の不溶化を充分に抑制できず、また高すぎると嵩高となり、一カプセル当りの主薬の含有比が低下したりあるいはカプセルサイズを大きくせざるをえない等の弊害が生じるので、いずれにして好ましくない。本カプセル剤は、所望により、通常、硬ゼラチンカプセル剤を調製する際に使用され得る慣用の崩壊剤、賦形剤、結合剤、溶解助剤、静電除去剤、滑沢剤、コーティング剤、光安定化剤等を含有し得る。

【０００９】崩壊剤としては、例えば部分α化デンプン、カルボキシメチルスターチナトリウム、カルボキシメチルセルロースカルシウム（ＣＭＣカルシウム）、低置換度ヒドロキシプロピルセルロース（ＬＨＰＣ）、クロスカルメロースナトリウム（例、Ac-Di-Sol，旭化成

（株））、ポリビニルポリピロリドン等が例示されるが、好ましくは、ＣＭＣカルシウム、ＬＨＰＣ等である。崩壊剤の含量は、カプセル剤全体に対して通常、約１～６０重量％、好ましくは約３～４０重量％、さらに好ましくは約５～２０重量％である。カプセル全充填物に対しては、約２～７０重量％、好ましくは約５～５０重量％、さらに好ましくは約１０～３０重量％である。カプセル剤皮に対しては、約１０～１００重量％、好ましくは約２０～９５重量％、さらに好ましくは約３０～９０重量％である。賦形剤としては、例えば乳糖、白糖、Ｄ－マンニトール、コーンスターチ、バレイショデンプン、ヒドロキシプロピルスターチ等が例示されるが、好ましくはＤ－マンニトール、コーンスターチ等ある。賦形剤の含量は、カプセル剤全体に対して通常、約１０～９０重量％、好ましくは約２０～７０重量％、さらに好ましくは約３５～６０重量％である。カプセル全充填物に対して通常、約３０～９５重量％、好ましくは約４０～８５重量％、さらに好ましくは約４５～８０重量％である。結合剤としては、例えばメチルセルロース、ポリビニルピロリドン、ヒドロキシプロピルセルロース（ＨＰＣ）、ポリビニルアルコール、ゼラチン、デキストリン等が例示されるが、好ましくはＨＰＣである。結合剤の含量は、カプセル全充填物に対して、通常、約０．５～１０重量％、好ましくは約１～５重量％である。溶解助剤としては、例えばコハク酸が例示される。溶解助剤の含量は、カプセル全充填物に対して、通常、約１～５重量％である。静電除去剤としては、シリカ（例：カープレックス（シオノギ）、アエロジル（日本アエロジル（株））が例示される。静電除去剤の含量は、カプセル全充填物に対して、通常、約0．１～１重量％である。

【００１０】滑沢剤としては、ステアリン酸マグネシウム、タルク、ショ糖脂肪酸エステルなどが例示される。コーティング剤としては、ポリビニルアセタールジエチルアミノアセテート、アクリル酸エチル・メタアクリル酸メチル共重合体、アミノアルキルメタアクリレートコポリマー、ヒドロキシプロピルメチルセルロースアセテートサクシネート、ヒドロキシプロピルメチルセルロースフタレート、マクロゴール等が例示される。光安定化剤としては、酸化チタン等が例示される。本カプセル剤は、上記原料を用いて、混合、練合、製粒、乾燥、調粒、滑混、カプセル充填等の操作を当該分野で周知の方法に準じて行うことにより製造できる。カプセルとしては、好ましくは日本薬局方に規定の３号または４号カプセルが使用される。

【００１１】本カプセル剤における主薬溶出性の改善の程度は、種々の溶出試験により実証され得るが、例えば後記試験例に記載のごとく第１２改正日本薬局方等に規定の溶出試験法によって示される。例えば主薬として前記化合物１を含む本カプセル剤を、４０℃／相対湿度７

５％開放の条件下で３ケ月間保存した場合でも、該溶出試験（条件：第２法（パドル法），５０ｒｐｍ，第２液（ｐＨ約６．８））による試験開始後２０分後の化合物１の溶出率を、好ましい態様として、カプセル内の主薬含量に対して少なくとも６０％または７０％以上、特に好ましくは８５～９５％のレベルに維持できる。一方、同条件下でアミノ酢酸を含有しない対照製剤を保存した場合には、２０分後の化合物１の溶出率は４０％以下となり、保存当初の製剤と比べて大幅に低下する。すなわち、化合物１は、本カプセル剤においてアミノ酢酸を配合させることにより、例えば２０分後の溶出率を２倍以上に改善できる。化合物１を含有する本カプセル剤の好ましい態様としては、カプセル剤皮に対して、化合物１を約１０～５０重量％、アミノ酢酸を約１～２０重量％、崩壊剤を約３０～６０重量％含有し、さらに好ましくは化合物１を１５～３５重量％、アミノ酢酸を３～１５重量％、崩壊剤を３５～５５重量％含有し、特に好ましくは化合物１を２０～３０重量％、アミノ酢酸を５～１０重量％、崩壊剤を４０～５０重量％含有する。

【００１２】同様に前記化合物２を含む本カプセル剤を、４５℃／密栓の条件下で３ケ月間保存した場合でも、該溶出試験（条件：第２法（パドル法），５０ｒｐｍ，ｐＨ４．０緩衝液）による２０分後の化合物２の溶出率は、好ましい態様として、６０％または７０％以上、特に好ましくは８０～９０％のレベルに到達する。一方、同条件下でアミノ酢酸を含有しない対照製剤を保存した場合には、試験開始後２０分後の化合物２の溶出率は約４５％となり、保存当初の製剤と比べて大幅に低下する。すなわち、化合物２は、本カプセル剤において、アミノ酢酸を配合させることにより、例えば２０分後の溶出率を約１．５倍以上、好ましくは約１．８倍以上に改善できる。化合物２を含有する本カプセル剤の好ましい態様としては、カプセル剤皮に対して、化合物２を約６０～１００重量％、アミノ酢酸を約１～２０重量％、崩壊剤を約６０～９０重量％含有し、さらに好ましくは化合物２を約７０～９０重量％、アミノ酢酸を約１～１５重量％、崩壊剤を約６５～８５重量％含有し、特に好ましくは化合物２を約７５～８５重量％、アミノ酢酸を１～１０重量％、崩壊剤を７０～８０重量％含有する。

【００１３】

【実施例】以下に本発明の実施例を示すが、これらは本発明をなんら制限するものではない。試験化合物としては以下のものを用いた。

化合物１：２－（イソオキサゾール－３－イル）－１，６，７，９－テトラヒドロイミダゾ[４，５－ｄ]ピラノ[４，３－ｂ]ピリジン・１リン酸・１水和物

化合物２：（２Ｓ－シス）－３－アセトキシ－５－[３－（４－（２－メトキシフェニル）－１－ピペラジニル）プロピル]－２，３－ジヒドロ－２－（４－メトキシフェニル）－８－クロロ－１，５－ベンゾチアゼピン－４（５Ｈ）－オン・１クエン酸

実施例１

（処方）化合物１、アミノ酢酸等を含むすべてのカプセル内包成分を混合し、乾式粉末充填法によりカプセルに充填した（以下、カプセルＡという）。その組成を表1に示す。なお対照製剤として、アミノ酢酸を配合しない他はカプセルＡ全く同じ組成のカプセルＢ（４号カプセル、合計１６５．０ｍｇ）を調製した。

【００１４】

【表１】

（カプセルA）

成分	含量（mg）
化合物１	10.0
結晶セルロース PH101	66.2
コーンスターチ	28.38
CMC カルシウム	18.75
カープレックス 67（シオノギ）	0.42
ステアリン酸Ｍｇ	1.25
アミノ酢酸	3.0
4号空カプセル	40.0
合計	168.0

（溶出試験）上記カプセルＡおよびＢについて、40℃、RH(相対湿度)75%開放の条件下、3ケ月保存したときの化合物１の溶出曲線を、それぞれ図1および図２に示す。試験条件：第１２改正日本薬局方溶出試験法　第２法(パドル法)　回転数50rpm、第２液(pH約6.8，温度37℃)

（結果）アミノ酢酸を添加しないカプセルＢでは、保存初期に比べて３ケ月後の溶出率は著しく遅延し、１０分後から徐々に溶出しだして例えば２０分後の溶出率は３５％にとどまり、６０分後にようやく９０％が溶出した。一方、アミノ酢酸を添加したカプセルＡでは、５分後には溶出しだして、２０分後には９１％の溶出率に達した。すなわちアミノ酢酸の添加により、硬ゼラチンカプセル剤の不溶化が顕著に抑制されて、溶出率が改善されることがわかった。

【００１５】実施例２

（処方）化合物２、低置換度ヒドロキシプロピルセルロース（LHPC31）、Ｄ－マンニトールおよびコハク酸を、ヒドロキシプロピルセルロース（HPC SL）水溶液で湿式造粒、乾燥、調粒した後、ステアリン酸マグネシウムを滑混する時にアミノ酢酸も同時に混合してカプセルに充填した（カプセルＣ）。その組成を表２に示す。なお対照製剤として、アミノ酢酸を配合しない他は、カプセルＣ全く同じ組成のカプセルＤ（３号カプセル、合計２３０．０ｍｇ）を調製した。

【００１６】

【表２】

（カプセルＣ）

成分	含量（mg）
化合物２	40.0
LHPC31	36.6
D-マンニトール	92.2
コハク酸	5.0
HPC SL（液添加）	5.0
アミノ酢酸（外添加）	2.0
ステアリン酸Ｍｇ（外添加）	1.8
３号空カプセル	50.0
合計	232.0

（溶出試験）上記カプセルＣおよびＤについて、45℃密栓　の条件下、3ヶ月保存したときの化合物２の溶出曲線を、それぞれ図３および図４に示す。

試験条件：第１２改正日本薬局方溶出試験法　第２法(パドル法)　回転数50rpm、酢酸緩衝液(pH4.0、温度37℃)

（結果）アミノ酢酸を添加しないカプセルＤでは、保存初期に比べて３ケ月後の溶出率は著しく遅延し、５分後から徐々に溶出しだして例えば２０分後の溶出率は４３％にとどまり、６０分後でも８０％には到達しなかった。一方、アミノ酢酸を添加したカプセルＣでは、試験開始後すぐに溶出しだして、２０分後にはすでに８４％の溶出率に達した。すなわちアミノ酢酸の添加により、硬ゼラチンカプセルの不溶化が顕著に抑制されて、溶出率が改善されることがわかった。

【００１７】

【発明の効果】本カプセル剤は、アミノ酢酸を含有していることによりカプセル剤皮の不溶化が抑制されており、加温、加湿条件下で長期保存したとしてもカプセル自体の経時変化が少なく、内包薬物の著しい溶出遅延は認められない。また、アミノ酢酸は、タンパク質のような高分子物質と比べてそれ自身が非常に安定でかつ水溶性の高い物質であり、カプセルに内包させても製剤特性への悪影響は懸念されない。

【図面の簡単な説明】

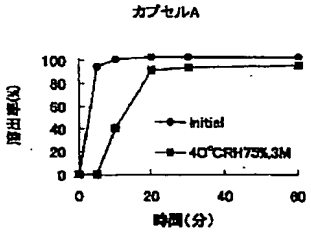
【図１】アミノ酢酸を含有する化合物１の硬ゼラチンカプセル剤について、主薬の溶出性の経時変化を示すグラフである。

【図２】アミノ酢酸を含有しない化合物１の硬ゼラチンカプセル剤について、主薬の溶出性の経時変化を示すグラフである。

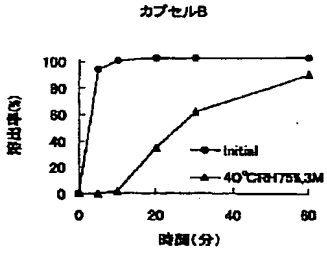
【図３】アミノ酢酸を含有する化合物２の硬ゼラチンカプセル剤について、主薬の溶出性の経時変化を示すグラフである。

【図４】アミノ酢酸を含有しない化合物２の硬ゼラチンカプセル剤について、主薬の溶出性の経時変化を示すグラフである。

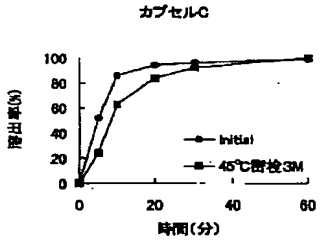
【図１】



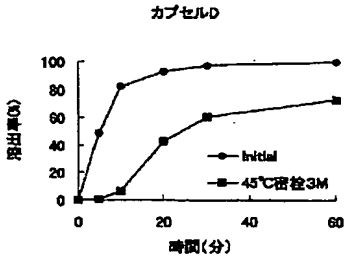
【図２】



【図３】



【図４】



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